

Prescription for Trouble

By Sen. Tom Coburn, MD and Scott Gottlieb, MD
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FDA can finally prevent narcotic drugs that can be widely abused from easily threatening patient safety. Will it seize the moment?

Abuse of prescription narcotics remains one of America's fastest growing drug problems. But rates of illicit use of some prescription opioids like OxyContin — drugs that have been subject to the most rampant abuse — are finally starting to decline.



Stepped-up enforcement against illegal diversion is one reason. More significant are changes in the medicines themselves. New technologies make the drugs less prone to manipulation and therefore much less likely to be used illegally in the first place.

Some of the most widely abused drugs, including OxyContin, have been re-engineered in tamper-resistant formulations and introduced in place of their original versions. Rates of abuse have fallen sharply as a consequence.

But the Food and Drug Administration (FDA) may let the older, riskier versions back onto the market in the form of cheap generic drugs — reigniting the original problems. Ample evidence shows that criminal use will simply shift to the generic drugs, since these older pills are easier to abuse. It will undermine efforts undertaken by industry and policymakers to design the new tamper-resistant drugs as a way to combat the problem.

The FDA argues that its hands may be tied. In order to keep older drugs off the market, FDA has to declare that they were withdrawn for safety reasons after the tamper-resistant versions came along. FDA was asked to make this declaration when the tamper-resistant drugs were first introduced. But the Obama administration's lawyers at the Department of Health and Human Services and FDA are wrangling over whether FDA has the proper authority.

As we'll explain, FDA's handwringing over what it calls "complex and novel legal issues"¹ is partly a problem of the agency's own making. FDA must decide one way or another. We think the agency's delay only exacerbates the risks to public health.

A History of Abuse

At issue are long-acting, oral opioid drugs that are used to treat chronic pain from conditions like metastatic cancer. FDA approved the original OxyContin in 1995 for use as an analgesic in people with

moderate to severe pain requiring relief for several days or more. Another manufacturer sells a similar drug under the brand name Opana ER. It was known that these drugs would have a risk of abuse because of their properties as a narcotic, and so they've been placed in Schedule II of the Controlled Substances Act (which places certain restrictions on medicines that have a high potential for abuse, for example requiring doctors to write for only limited doses of pills at a time and to use special prescription pads that allow for easier tracking). What nobody foresaw in 1995 was how rampant the illicit use would become once abusers discovered how to tamper with the drug.

These drugs contain a high dose of the narcotic oxycodone. The formulations encase this active ingredient in a time-release mechanism that allows it to trickle into the bloodstream over 12 hours. That's what gives the pills the long-acting attributes.

At the time that the products were first introduced, it was thought that the long-acting formulation would help to reduce the opportunity for abuse.² Shortly after the release of OxyContin in 1995, drug abusers discovered they could break the time-release mechanism by simply crushing the pills (so-called "dose dumping"). This enabled the entire dose of oxycodone to be absorbed immediately, either through injecting or snorting. It gives a fast, more powerful euphoric effect that mimics a heroin-like "high."

Will FDA Action Thwart Progress?

At the prompting of FDA and Congress,³ the manufacturers of OxyContin and Opana ER reformulated their pills to make them crush- and tamper-resistant. The new versions make it harder for the active narcotic ingredient to be dose dumped.

At the same time, and also with FDA's urging, these same manufacturers removed their older, abuse-prone formulations from the market in the United States and Canada. The tamper-resistant versions of some of the most commonly prescribed opioid medicines have now fully supplanted the original, abuse-prone formulations.

Data from clinical trials and real-world use show that these tamper-resistant drugs make illicit use more difficult.⁴ Rates of abuse of these re-formulated drugs have started declining as a result. But a regulatory action that FDA is poised to take could inadvertently undermine these public health gains.

Multiple generic drug manufacturers are seeking FDA permission to market non-tamper-resistant versions of the original formulation of OxyContin. Similarly, there are already FDA-approved generic versions of the original formulation of Opana ER, the highest strengths of which are poised for launch in the United States in January 2013.

The question is whether FDA has the discretion to block the entry of these now-inferior generic products by determining that their "reference" products — the older versions of the opioid drugs that lacked the tamper resistance — were withdrawn for safety reasons. FDA has had years to make this decision. It has run out of time.

Policymakers pressed the drug makers to come up with these tamper-resistant formulations as one way to combat diversion and abuse. It was rightly hoped that these new formulations could become one tool in combating illicit diversion and abuse. It worked. Now that these new technologies are available, enabling the market to be simultaneously served by the older opioid drugs (that lack the abuse-deterrent features) defeats the purpose of the tamper-resistant formulations.

Under current law, to block the entry of generic drugs, FDA has to issue a finding stating that the original formulations were withdrawn from the market for safety reasons.⁵ Such a judgment would comport with the practical circumstances surrounding the introduction of the tamper-resistant formulations in the first

place. Part of FDA's rationale in pressing for the development of the new products was so these abuse-resistant versions would take the place of the riskier formulations.

Manufacturing Trouble

FDA has said that it is struggling with how to retrospectively "deem" the original formulation of these drugs "withdrawn from the market for reasons of safety," especially when the labels of the new formulations do not contain language that suggests that the new tamper-resistant drugs are any better than the older versions.

The legal questions that have FDA hamstrung are partly a result of the agency's own decisions. FDA has helped to tie its own hands.

On the issue of timing: FDA says it may be hard to "retroactively" make the declaration that the original opioid formulations are no longer safe. But FDA was first asked to withdraw the older versions of these drugs for safety reasons at the time that their original manufacturers stopped selling these medicines.

The agency didn't respond to these original requests. It should have. Regulations give FDA ample discretion to decide "whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons... at any time after the drug has been voluntarily withdrawn from sale."⁶

On the issue of labeling: it's true the labels of the tamper-resistant opioids don't identify these abuse-deterrent properties. That's also a problem FDA manufactured.

Part of the agency's fears? That putting these claims on drug labels might encourage more use of these narcotics by giving doctors a false sense that the drugs are now safer. FDA hasn't established a standard definition of what it means for a drug to be "tamper resistant" and how a manufacturer can make such a claim.

FDA's concern with allowing these claims is ironic. After all, the re-introduction of the older formulations is likely to do a lot more to encourage illicit use than any marketing language FDA might have let manufacturers use to advertise the abuse-deterrent drugs. Right now, FDA suggests that drug makers need to show that the overall burden of addiction in a "community" is reduced in order to claim that an opioid is resistant to abuse. This may be an insurmountable standard.

Finally, on FDA's question of whether or not it can withdraw a drug for safety reasons, if most of those safety problems involve the drug's illicit use: FDA is concerned that it lacks sufficient evidence to judge the older formulations (the drugs without tamper-resistant technologies) to be unsafe. The agency's argument is that by all evidence, OxyContin is largely safe when carefully used as prescribed. So how can FDA say that the older drugs are so "unsafe" that they had to be withdrawn?

But FDA has already said that when it comes to these older opioid drugs that lack the tamper-resistant technologies, it is not only worried about illicit use but problems from misuse even by well-meaning patients. This includes situations where patients or health care providers try to crush tablets to make them easier to swallow, and inadvertently defeat the slow-release coatings — or situations where children may come upon the pills and chew the tablets prior to an accidental ingestion, enabling a dangerous dumping of the full dose of narcotics.

There already is precedent for FDA worrying about the inappropriate use of opioid products when judging whether a drug is safe for continued marketing. In July 2005, FDA demanded the withdrawal of the tamper-resistant opioid Palladone because of concerns about its safety. It turned out that mixing the pills (deliberately or accidentally) with alcohol caused a dumping of the active ingredient, the narcotic analgesic

hydromorphone. FDA saw this as a big safety risk.⁷ The agency either has the authority to worry about these issues or it doesn't. But it needs to be consistent.

The Need for Swift Action

Right now, Canada is poised to allow the introduction of generic versions of oxycodone into its own market, creating the possibility that these drugs will be illegally diverted into the United States.⁸ The White House Office of National Drug Control Policy already warned law enforcement to be on the lookout for cheap copies of OxyContin, which it said could hit the Canadian market as soon as next month. "The potential exists for diversion into the United States because the old formulations, which are easier to abuse, are unavailable in the United States," said the notice.⁹

There's ample precedent for new formulations of a drug to offer such an improvement in safety over prior versions, that the older formulations are no longer deemed safe relative to their more modern alternatives. The market for vaccines and biologics is rife with examples where newer drug versions were formulated in a way to make them substantially safer than the alternatives they obsoleted.

There are also similar precedents when it comes to hypnotic and analgesic drugs. For example, in 1993 FDA told the maker of the hypnotic anesthetic drug propofol to reformulate the medicine in order to address safety issues. Once the new version of the drug was available, FDA refused to let generics copy the original formulation.

FDA needs to act with timeliness, candor, and integrity on the scope of its authority and what it can and can't do. If it needs new authority to make these determinations, it must tell Congress right away.

Allowing the market to be flooded with cheap, generic versions of outdated formulations will only feed the problems that we have begun to resolve with better technology. The creation of abuse-deterrent formulations fulfilled an important public health goal. Policymakers demanded the creation of these new drugs. We should leverage the benefits of this technology, and not undermine its purpose.

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Footnotes:

1. FDA, Defendant's Response to the Court's November 30, 2012 Order. Brief filed before the United States District Court for the District of Columbia, in *Endo Pharmaceuticals Inc. v. United States Food and Drug Administration, et al.* December 3, 2012
 2. Theodore J. Cicero, James A. Inciardi, and Alvaro Muñoz. Trends in Abuse of OxyContin® and Other Opioid Analgesics in the United States: 2002-2004. *The Journal of Pain*, Vol 6, No 10 (October), 2005: pp 662-672
 3. In 2006, Congress stated that FDA "providers and patients alike will benefit from the expedited review of safer drugs, as well as the provision of information that accurately differentiates abuse-resistant formulations." H.R. Rep. No. 109-102 (2006)
 4. Cicero, et al., Effect of Abuse-Deterrent Formulation of OxyContin, *N Engl J Med* 2012; 367:187-189
 5. 21 U.S.C 355(j)(6) states that FDA has to withdraw or suspend the approval of any application for a generic medicine when the reference product upon which the application is based "has been withdrawn from sale for safety... reasons."
 6. 21 C.F.R. 314.161(a)(1),(2)
 7. FDA's press release stated "serious and potentially fatal adverse reactions can occur when Palladone (hydromorphone hydrochloride) extended release capsules are taken together with alcohol."
 8. Susan Lunn. Generic oxycodone from Canada has U.S. officials on alert. *CBC News*, December 5, 2012. Available [here](#).
 9. Devlin Barrett, Thomas Catan, and Paul Vieira. U.S. on Alert for Canadian Drugs. *The Wall Street Journal*, December 4, 2012. Available [here](#).
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